light of these amendments and the following remarks.

I. Finality of Restriction Requirement

The Examiner has made final the Restriction Requirement as set forth in the Communication mailed September 25, 2001. Accordingly, in an earnest effort to advance the prosecution of this case, Applicants have canceled claims 7-11, 13 and 14, without prejudice. However, in light of the finality of this Restriction Requirement, Applicants reserve the right to file a divisional application to the canceled subject matter.

II. Rejection of Claims 1-6 and 12 under 35 U.S.C. § 112, second paragraph

Claims 1-6 and 12 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner suggests that these claims are rendered vague and indefinite in the recitation of Lng108 because this is a laboratory designation, the meaning of which is unknown. Applicants respectfully traverse this rejection.

As mandated by MPEP § 2173, definiteness of claim language must be analyzed, not in a vacuum, but in light of: (A) The

content of the particular application disclosure; (B) The teachings of the prior art; and (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. Lng108 is described consistently in the specification as follows:

> Lng108 refers, among other things, to native proteins expressed by the gene comprising the polynucleotide sequence of SEQ ID NO:1 or 2. The deduced amino acid sequence of a polypeptide encoded thereby is depicted in SEQ ID NO:3. By "Lng108" it is also meant herein polynucleotides which, due to degeneracy in genetic coding, comprise variations in nucleotide sequence as compared to SEQ ID NO: 1 or 2, but which still encode the same protein. In the alternative, what is meant by Lng108 as used herein, means the native mRNA encoded by the gene comprising SEQ ID NO:1 or 2 or it can refer to the actual gene comprising SEQ ID NO:1 or 2, or levels of a polynucleotide which is capable of hybridizing under stringent conditions to the antisense sequence of SEQ ID NO:1 or 2.

See specifically, page 4, lines 14-27 and page 6, line 24 through page 8, line 3. Thus, what is meant by Lng108 in the claims would be clear and definite to one of skill in the art when read in light of the content of this particular application disclosure.

However, in an earnest effort to advance the prosecution of this case, Applicants have amended the claims in accordance with the Examiner's recommendation and the teachings of the specification to specify that Lng108 comprises a polynucleotide

of SEQ ID NO:1 or 2, a polynucleotide which hybridizes under stringent conditions to an antisense sequence of SEQ ID NO:1 or 2, or a protein expressed by a polynucleotide sequence of SEQ ID NO:1 or 2. No new matter has been added by this amendment.

Withdrawal of this rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested in light of this amendment.

III. Rejection of Claims 1-6 and 12 under 35 U.S.C. § 112, first paragraph

Claims 1-6 and 12 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, the Examiner suggests that there are discrepancies between the sequences contained in the CRF and the specification. In particular, the Examiner suggests that while the specification teaches that Lng108 and nucleotides encoding it are the same as staniocalcin and staniocalcin precursor, SEQ ID NO:1 and 2 are different from the nucleotide sequence encoding staniocalcin as set forth in GenBank Accession Number HSU25997.

Applicants respectfully traverse this rejection.

At page 4 of the instant application, it is taught that U.S.

Patent 5,877,290 and U.S. Patent 5,837,498 disclose a human Corpuscles of Stannius, staniocalcin polypeptide and the nucleic acid sequence encoding this polypeptide and that in the present invention, it has been found that this polypeptide and the nucleic acid encoding this polypeptide are diagnostic markers for cancer. Thus, as made clear in the instant specification, it is the staniocalcin polypeptide and nucleotide sequences taught in these U.S. Patents, not in GenBank Accession Number HSU25997 as suggested by the Examiner, to which Lng108 refers.

However, as discussed in Section II, *supra*, in an earnest effort to advance the prosecution and to clarify Lng108, the claims have been amended to specify that Lng108 comprises a polynucleotide of SEQ ID NO:1 or 2, a polynucleotide which hybridizes under stringent conditions to an antisense sequence of SEQ ID NO:1 or 2, or a protein expressed by a polynucleotide sequence of SEQ ID NO:1 or 2. Thus, any confusion relating to the fact that the prior art teaches multiple sequences referred to as staniocalcin is irrelevant to the claims as amended.

Applicants respectfully disagree with the Examiner's characterization of N residues in SEQ ID NO: 2 as a "large area of ambiguity" rendering the written description insufficient to support claims for the detection of Lng108 or the detection of

SEQ ID NO:2. SEQ ID NO:2 comprises a total of 3,762 nucleotides of which about 70 are set forth as N's. Accordingly, less than 2% of the sequence is unknown. Clearly providing over 98% of the nucleotide sequence of a 3,762 nucleotide base sequence conveys to one of skill in the art that Applicants had possession of the sequence and places the public in possession of the sequence. Thus, the instant specification satisfies the written description requirement as set forth in MPEP § 2163.

The Examiner also suggests that one of skill in the art would not know how to use the instant methods for the diagnosis of cancer because in 5 out of 18 primary lung cancer samples, the amplified polynucleotide was elevated in the normal tissue relative to the tumor tissue and in 3 out of 18 primary lung cancer samples the levels of amplified polynucleotide were not significantly different in adjacent normal tissue versus the tumor tissue.

Applicants respectfully traverse this rejection.

Claim 1 of the instant application is drawn to **diagnosing**, which is defined in Webster's Dictionary as the act or process of deciding the nature of a diseased condition by examination. Clearly, determining levels of Lng108 in cells, tissues or bodily fluids in a patient as taught in the instant application

constitutes an act or process of examination for deciding the nature of a diseased condition. Further, regardless of whether one of skill accepts the teachings of the specification that 67% (14 of 21) of the lung cancer samples exhibited overexpression of Lng108 or the Examiner's contention that 56% (10 of 18) of the lung cancer samples exhibited overexpression of Lng108, more than half of the lung cancer samples and cancer samples from other tissues exhibited elevated Lng108 expression levels. Thus, Lng108 clearly serves as a marker for deciding whether a patient has cancer. Accordingly, the teachings of the specification are enabling for claims drawn to diagnosing cancer via detection of Lng108 levels.

Further, Applicants are submitting herewith a Declaration under 37 C.F.R. § 1.132 by Dr. Nam Kim describing additional experiments confirming Lng108 to be a lung cancer diagnostic marker and a general cancer diagnostic marker. Using a standard ELISA such as described at, line 24 through page 13, line 16, of the instant specification, it was confirmed that Lng108 protein is elevated at least two-fold in serum samples of patients with breast, colon, lung and prostate as compared to normal serum samples and at least 5-fold in the majority of the cancers examined. See paragraphs 5 and 6 of Dr. Kim's Declaration, as

well as the scattergram attached to Dr. Kim's Declaration. At page 8, line 32, through page 9, line 3, of the specification, it is taught that for a quantitative diagnostic assay a positive result indicating the patient being tested has cancer is one in which cells, tissues, or bodily fluid levels of a cancer marker, such as Lng108, are at least two times higher, and most preferable are at least five times higher, than in preferably the same cells, tissues, or bodily fluid of a normal human control. Thus, the ability of Lng108 to serve as a diagnostic marker for cancer as taught in the instant application is clearly confirmed by additional experiments described in Dr. Kim's Declaration.

Applicants also respectfully disagree with the Examiner's suggestion that the specification provides no support as to staging and monitoring of change in stage of cancer. The Examiner suggests that the specification does not link the data in Table 2 with a stage of cancer. However, as taught at page 25 of the specification, lines 9-21, the comparison of mRNA expression levels in cancer sample versus isogenic normal adjacent tissue from the same individual set forth in Table 2 provides an indication of the specificity for the cancer stage. Specifically, higher levels of mRNA expression were observed in the cancer sample as compared to the normal adjacent tissue.

Thus, while specific stages may not be mentioned, as would be understood by one of skill in the art upon reading this disclosure, higher levels of mRNA expression are indicative of more advanced stages of cancer.

Further, the ability of Lng108 to serve as marker for various stages of cancers is confirmed by experiments set forth in Dr. Kim's Declaration. As stated in paragraph 4 of Dr. Kim's Declaration, cancer serum samples analyzed consisted of samples from patients with all stages and grades of the tumor. As discussed in paragraph 6 of Dr. Kim's Declaration, at least a 2-fold increase in mean Lng108 protein concentrations was observed in all cancer samples sets as compared to serum from normal controls and a 5-fold increase in mean Lng108 protein concentrations was observed in most of the cancer samples.

The test of enablement, as set forth in MPEP § 2164.01 is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The Examiner suggests that given the unreliability in this art field and the lack of teachings in the specification, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to diagnose or monitor metastatic cancer. Applicants respectfully disagree.

The specification provides a detailed exemplary method routine to those of skill in the art for detecting Lng108 levels as claimed. Accordingly, one of skill in the art can determine Lng108 levels in a patient in accordance with the teachings of the specification without any experimentation whatsoever. Further, one can routinely compare their measured Lng108 levels to varying Lng108 levels taught in the specification to determine if Lng108 levels are elevated, again without any experimentation whatsoever. If elevated to levels comparable with over 50% of the cancer samples taught in the specification, an act or process of examination for deciding the nature of a diseased condition, better known as a diagnosis, can be made. If the measured Lng108 levels are inconclusive, the skilled diagnostician can perform one or more additional diagnostic tests not considered to be undue but rather in accordance with well-accepted practices for diagnosis of a disease.

Claim 6 has been canceled by this amendment thus mooting the Examiner's rejection with respect to this claim.

It is respectfully requested that the rejection under 35 U.S.C. § 112, first paragraph be withdrawn in light of the amendments to the claims and the above arguments.

IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"VERSION WITH MARKINGS TO SHOW CHANGES MADE."**

Respectfully submitted,

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Date: **July 22, 2002**

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please cancel claims 6-11, 13 and 14, without prejudice.

Please amend the claims as follows:

1. (amended) A method for diagnosing the presence of cancer in a patient comprising:
(a) determining levels of Lng108 in cells, tissues or bodily fluids in a patient; and
(b) comparing the determined levels of Lng108 with levels of Lng108 in cells, tissues or bodily fluids from a normal human control, wherein a change in determined levels of Lng108 in said patient versus normal human control is associated with the presence of cancer and wherein Lng108 comprises a polynucleotide of SEQ ID NO:1 or 2, a polynucleotide which hybridizes under stringent conditions to an antisense sequence of SEQ ID NO:1 or 2, or a protein expressed by a polynucleotide sequence of SEQ ID NO:1 or 2.

2. (amended) A method of diagnosing metastases of cancer in a patient comprising:
(a) identifying a patient having cancer that is not known to have metastasized;
(b) determining Lng108 levels in a sample of cells, tissues, or bodily fluid from said patient; and
(c) comparing the determined Lng108 levels with levels of Lng108 in cells, tissue, or bodily fluid of a normal human control, wherein an increase in determined Lng108 levels in the patient versus the normal human control is associated with a cancer which has metastasized and wherein Lng108 comprises a polynucleotide of SEQ ID NO:1 or 2, a polynucleotide which hybridizes under stringent conditions to an antisense sequence of SEQ ID NO:1 or 2, or a protein expressed by a polynucleotide sequence of SEQ ID NO:1 or 2.

3. (amended) A method of staging cancer in a patient having cancer comprising:
(a) identifying a patient having cancer;
(b) determining Lng108 levels in a sample of cells, tissue, or bodily fluid from said patient; and
(c) comparing determined Lng108 levels with levels of Lng108 in cells, tissues, or bodily fluid of a normal human control,

wherein an increase in determined Lng108 levels in said patient versus the normal human control is associated with a cancer which is progressing and a decrease in the determined Lng108 levels is associated with a cancer which is regressing or in remission and wherein Lng108 comprises a polynucleotide of SEQ ID NO:1 or 2, a polynucleotide which hybridizes under stringent conditions to an antisense sequence of SEQ ID NO:1 or 2, or a protein expressed by a polynucleotide sequence of SEQ ID NO:1 or 2.

4. (amended) A method of monitoring cancer in a patient for the onset of metastasis comprising:

(a) identifying a patient having cancer that is not known to have metastasized;

(b) periodically determining levels of Lng108 in samples of cells, tissues, or bodily fluid from said patient; and

(c) comparing the periodically determined Lng108 levels with levels of Lng108 in cells, tissues, or bodily fluid of a normal human control, wherein an increase in any one of the periodically determined Lng108 levels in the patient versus the normal human control is associated with a cancer which has metastasized and wherein Lng108 comprises a polynucleotide of SEQ ID NO:1 or 2, a polynucleotide which hybridizes under stringent conditions to an antisense sequence of SEQ ID NO:1 or 2, or a protein expressed by a polynucleotide sequence of SEQ ID NO:1 or 2.

5. (amended) A method of monitoring a change in stage of cancer in a patient comprising:

(a) identifying a patient having cancer;

(b) periodically determining levels of Lng108 in cells, tissues, or bodily fluid from said patient; and

(c) comparing the periodically determined Lng108 levels with levels of Lng108 in cells, tissues, or bodily fluid of a normal human control, wherein an increase in any one of the periodically determined Lng108 levels in the patient versus the normal human control is associated with a cancer which is progressing in stage and a decrease is associated with a cancer which is regressing in stage or in remission and wherein Lng108 comprises a polynucleotide of SEQ ID NO:1 or 2, a polynucleotide which hybridizes under stringent conditions to an antisense sequence of SEQ ID NO:1 or 2, or a protein expressed by a polynucleotide sequence of SEQ ID NO:1 or 2.

12. (amended) The method of claim 1, 2, 3, 4~~,~~ or 5~~, 6, 7,~~

~~8, 9, 10 or 11~~ wherein the cancer is lung cancer.